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Original Research

Hydroxychloroquine in combination with platinum doublet chemotherapy as first-line treatment for extensive-stage small cell lung cancer (Study 15): A randomised phase II multicentre trial☆

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ABSTRACT

Background: Most patients with small-cell lung cancer (SCLC) present with extensive-stage (ES) disease and have a poor prognosis despite achieving high initial response rates to platinum-based doublet chemotherapy. This study evaluated whether adding hydroxychloroquine (HCQ) to chemotherapy could improve outcomes.

Methods: This was a randomised multicentre phase II trial. Eligible patients had untreated ES-SCLC, a performance status 0–2 and measurable disease. Patients were randomly assigned (1:1 ratio) to HCQ (400 mg orally twice daily) plus carboplatin-gemcitabine or carboplatin–etoposide alone. Chemotherapy was administered for up to six cycles, with HCQ given concurrently and then as single agent for up to 30 months. Primary endpoint was PFS, aiming for a hazard ratio (HR) of 0.70.

Results: 72 patients were randomised (36 HCQ+chemotherapy and 36 chemotherapy alone). Median HCQ treatment duration was 4.4 months. HCQ did not improve PFS (HR 1·12 95 %CI 0·69–1.84; p = 0·64), with a median of 5.7 months (HCQ+chemotherapy) versus 6.2 months (chemotherapy). The corresponding median OS were 8.9 and 10.2 months (HR 0.83, 95 %CI 0.48–1.45, p = 0.52). Fewer patients in the HCQ arm completed four cycles of chemotherapy due to adverse events (64 % vs. 81 %). Grade ≥ 3 adverse events were higher in the HCQ+chemotherapy arm (83.3 % vs. 27.8 %), primarily anaemia, neutropenia, and thrombocytopenia, partly due to the initially higher gemcitabine dose used

Conclusions: Combining HCQ with platinum doublet chemotherapy did not improve PFS or OS outcomes for ES-SCLC, resulting in more patients stopping chemotherapy due to increased adverse events. When considered

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alongside other randomised studies of HCQ in cancer, the evidence collectively indicates a limited role for HCQ as a therapeutic option.

1. Introduction

Platinum-based chemotherapy with etoposide has been the primary first-line treatment for limited and extensive-stage small cell lung cancer (SCLC). Modest improvements in overall survival (OS) were seen only recently with the use of immune checkpoint inhibitors in combination with chemotherapy for ES-SCLC, including atezolizumab and durvalumab [1–5]. Despite achieving high initial response rates, most patients relapse within a year [6]. Previous novel treatments for SCLC, including anti-angiogenic therapies, have been unsuccessful.[7]

There has been interest in targeting autophagy to selectively kill cancer cells [8]. Autophagy, a lysosomal degradation pathway, eliminates cytosolic proteins, macromolecules, organelles, and protein aggregates. This is exploited by cancer cells to survive by generating nutrients and energy during periods of hypoxia and stress induced by chemotherapy. Induction of autophagy has been proposed as a mechanism of drug resistance that promotes cancer cell survival via self-digestion [9–11]. Pre-clinical studies showed that inhibitors of autophagy, like chloroquine and hydroxychloroquine (HCQ), may enhance anticancer agent activity [9,12]. However, pre-clinical and small early-phase clinical studies of chloroquine and HCQ have shown mixed results. [13–15].

There is an obvious appeal in finding effective anti-cancer therapies using repurposed, off-patent and affordable drugs. We designed Study 15 to evaluate HCQ for treating SCLC when combined with platinum doublet chemotherapy. This trial was conducted before checkpoint inhibitors were approved into routine use in the UK in December 2020. However, it is the first and only clinical trial of an autophagy inhibitor in SCLC and, more importantly, one of the few randomised studies of HCQ in any cancer type.

2. Patients and methods

We conducted an open-label randomised phase II trial (Study 15). Eligible patients were aged at least 18 years, with pathologically confirmed SCLC, extensive-stage disease, Eastern Co-operative Oncology Group (ECOG) performance status of 0–2, life expectancy greater than 8 weeks, adequate renal, hepatic and bone marrow function.

Patients were ineligible if they had treatment with chloroquine or related agents within the last year prior to randomisation; concurrent use of cytochrome P450 enzyme-inducing drugs; mixed histology; prior macular degeneration/diabetic retinopathy, history of glaucoma, medical history of prolonged QT interval, symptomatic brain metastases; or previous malignancy within three years. Ethical approval was obtained, and all patients provided informed written consent.

Patients were randomised (1:1) to receive platinum-based chemotherapy with or without HCQ. Minimisation was used with ECOG (0–1 vs 2), gender and intention to use consolidation mediastinal radiotherapy (yes or no/undecided) as stratification factors. Randomisation was done by site staff telephoning the central clinical trials office, who used a computer program to perform treatment allocation.

Patients randomised to the control arm received carboplatin and etoposide for up to six cycles (each cycle was three weeks). Carboplatin was given by IV on day 1, with the AUC5 dose calculated according to the Calvert formula. Etoposide was given by either IV 100mg/m^2 on days1–3 or IV 120mg/m^2 on day1 then oral capsules 100 mg twice daily on days2–3.

Patients randomised to the combination of HCQ plus chemotherapy, received oral HCQ 400 mg twice daily starting from day1 of chemotherapy. HCQ continued as single agent maintenance therapy after chemotherapy finished, for a maximum of 30 months from start of chemotherapy. HCQ was taken continuously until disease progression or unacceptable toxicities. The treating clinician could reduce the dose to 200 mg where appropriate. Chemotherapy consisted of carboplatin and gemcitabine on days 1 and 8, for up to six cycles. At the start of the trial, the dose of gemcitabine was 1250mg/m^2 IV, but this reduced to 1000mg/m^2 IV in October 2018 following haematological toxicities.

HCQ was given with gemcitabine instead of etoposide (a topoisomerase-2 inhibitor) because chloroquine and HCQ reduce the anti-tumour activity of etoposide when combined. HCQ intercalates into DNA and protects cancer cells against the killing activity of topoisomerase-2 inhibitors [16,17]. Furthermore, our previous randomised phase III trial demonstrated that carboplatin/gemcitabine chemotherapy has the same effect on OS and PFS as cisplatin/etoposide chemotherapy for treating extensive-stage SCLC [18]. Two independent review panels, from Cancer Research UK and the Independent Data Monitoring Committee (IDMC), agreed that using gemcitabine avoids the potential negative consequence for patients had we used etoposide in combination with HCQ.

All patients were assessed at baseline and at each chemotherapy visit, by clinical/physical examination and biochemistry. Chest/abdomen CT was performed at the end of cycles 2, 4 and 6, and a chest X-ray at the end of cycles 1, 3 and 5. Tumour response was assessed according to RECIST version 1.1. Visual acuity and fundoscopy assessment were performed at baseline and then if patient reported changes in vision. Health-related quality-of-life (QoL) was measured by the EORTC QLQ-C30 and the lung cancer module QLQ-LC13 at baseline, cycles 2, 4 and 6, then every 3–6 months after chemotherapy stopped.

3. Statistical analysis

The primary endpoint was PFS measured from randomisation to progression/death (whichever occurs first). Patients were censored at the date last known to be alive. Secondary endpoints included OS (time until death from any cause, otherwise censored at the last date known to be alive), best overall response rate (ORR, defined as a complete/partial tumour response), toxicities (NCI Common Toxicity Criteria version 4.0), QoL, and adherence.

The target accrual was 112 patients (93 PFS events), based on detecting improvement in median PFS from 6 months (chemotherapy only) to 8.5 months (chemotherapy plus HCQ), equivalent to a hazard ratio (HR) of 0.70, with 20 % one-sided statistical significance and 80 % power.

The database was locked in May 2023 after final follow-up data requested. Analyses were performed on an intention-to-treat basis. PFS and OS were examined using Kaplan-Meier curves and Cox regression to allow for the randomisation strata (ECOG, gender and disease status) and other factors. QoL was analyzed as repeated measures using a mixed model approach.

4. Results

72 patients were randomised between 7th April 2017 and 12th March 2020 (36 in each trial arm), from 13 UK hospitals (Fig. 1). Table 1 shows the baseline characteristics. Median age was 68 years, and 64 % and 21 % were ECOG 1 and 2 respectively. 14 patients (39 %) were recruited given the higher 1250mg/m^2 IV gemcitabine dose before the protocol amendment, and 22 patients (61 %) received the lower dose of 1000mg/m^2 IV.

The trial was stopped early by the IDMC in September 2020 for the following reasons: 1) The observed PFS HR was 1.11 from 72 patients

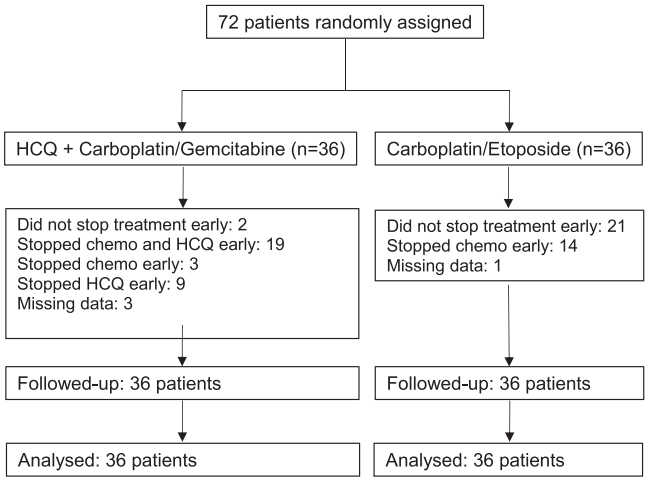

Fig. 1. CONSORT diagram of the Study 15 trial.

Table 1
Baseline characteristics.

		HCQ+chemotherapy N = 36 (%)	Chemotherapy alone N = 36 (%)
Age (Median; Range)		68.7 (50 −84)	66.5 (51 −86)
Age (years)	50 −59	8 (22.2)	4 (11.1)
	60 −69	12 (33.3)	22 (61.1)
	70 −79	13 (36.1)	8 (22.2)
	80 −89	3 (8.3)	2 (5.6)
Sex	Female	17 (47.2)	15 (41.7)
	Male	19 (52.8)	21 (58.3)
Smoker	Current Smoker	16 (44.4)	13 (36.1)
	Ex-Smoker	15 (41.7)	22 (61.1)
	Never Smoked	5 (13.9)	1 (2.8)
ECOG performance status	0	4 (11.1)	7 (19.4)
	1	25 (69.4)	21 (58.3)
	2	7 (19.4)	8 (22.2)
Intention to treat with consolidation mediastinal radiotherapy	Yes	4 (11.1)	4 (11.1)
	No/ Undecided	32 (88.9)	32 (88.9)

and the conditional power to detect a HR of 0.70 if the trial continued to the end was only 19%; 2) there was a noticeable higher percentage of adverse events (AEs) in the HCQ arm, some of which was due to the initial higher gemcitabine dose used, but the excess could not be ignored even though there was no biological rationale for a causal link to HCQ.

Fewer patients in the HCQ group completed at least four cycles of chemotherapy (64% vs. 81%); Supplementary Table 1. Seven (19%) patients in the HCQ group, stopped chemotherapy early due to AEs (compared to none in the chemotherapy alone arm). All 10 patients who completed six cycles of chemotherapy continued with maintenance HCQ. Median time from starting HCQ to stopping permanently was 4.4 (range 0.2–12.4) months. 47% (17/36) had a HCQ dose omission at any time due to AEs, patient/clinician decision, or disease progression. 11% (4/36) had a dose reduction to 200 mg due to AEs. 25% (9/36) stopped taking HCQ early due to AEs.

Table 2 summarises best tumour response data. In an intention-to-treat analysis, the percentage who had a complete/ partial response was 63.9% (HCQ and chemotherapy) versus 77.8% (chemotherapy alone), p = 0.20. For those who had evaluable disease, the corresponding complete and partial response rates were 74.2% vs. 84.8% (p = 0.29).

Median follow-up was 18 months. 67 patients progressed/died (32 in the HCQ group and 35 in the chemotherapy alone group); and 53

Table 2
Best tumour response.

	HCQ+chemotherapy N = 36 * (%)	Chemotherapy alone N = 36 (%)
Complete Response	1 (2.8)	2 (5.6)
Partial Response	22 (61.1)	26 (72.2)
Stable Disease	6 (16.7)	5 (13.9)
Progressive Disease	2 (5.6)	0 (0)
Missing	5 (13.9)	3 (8.3)
Complete Response/ Partial Response	*23 (63.9)*	*28 (77.8)*
Based on patients with evaluable disease	*N = 31*	*N = 33*
Complete Response/ Partial Response	*23 (74.2)*	*28 (84.8)*

patients died from any cause (24 in the HCQ group and 29 in the chemotherapy group).

There was no evidence that HCQ improved either PFS or OS. Median PFS was 5.7 months (95%CI 4.4–6.8) in those who had HCQ versus 6.2 months (5.2–6.8) in the chemotherapy alone group; Fig. 2. The unadjusted HR was 1.18 (95%CI 0.72–1.91, p = 0.51) and after adjustment the HR was 1.12 (95%CI 0.69–1.84, p = 0.64). To allow for the observed difference in baseline factors, the HR adjusted for age, sex, smoking status and ECOG was 1.33 (95%CI 0.77–2.31, p = 0.30).

Median OS was 8.9 months (95%CI 6.2–14.6) and 10.2 months (6.7–11.7) in the HCQ versus the chemotherapy group respectively; Fig. 2. 6-month OS rates were 70.2% (95%CI 51.7–82.8) for HCQ compared to 78% (95%CI 60.4–88.2) for chemotherapy alone. The unadjusted HR was 0.94 (95%CI 0.55–1.62, p = 0.83) and adjusted HR was 0.83 (95%CI 0.48–1.45, p = 0.52). To allow for the observed difference in baseline, the HR adjusted for age, sex, smoking status and ECOG was 0.95 (95%CI 0.52–1.73, p = 0.87).

PFS and OS subgroup analyses showed that HCQ was not beneficial for any baseline patient factors Supplementary Figs. 1 and 2).

More patients in the HCQ plus chemotherapy group had a reported AE of grade 3–4 (83.3 vs 27.8%); Supplementary Table 2. Most of these were grade 3. The excess was due to anaemia (41.7 vs 5.5%), neutropenia (30.6 vs. 8.3%) and thrombocytopenia (33.3 vs. 8.3%). Similar numbers of patients in HCQ group experienced anaemia and neutropenia regardless of whether they received the higher dose or not; Supplementary Table 3. However, 42.9% of patients who received the higher dose reported grade 3–4 thrombocytopenia compared with 27.3% in the lower dose. There were more reductions, delays, or omissions due to grade 3–4 haematological toxicities in the higher dose group compared with the lower dose group (50.0% vs 22.7%).

There were also more patients who had a reported serious adverse event (SAE) in the HCQ group compared to chemotherapy alone (66.7 vs 22.2%), of which 52.8 vs 22.2% were grade 3–5. The most common SAEs in the HCQ group were thrombocytopenia (27.8%), vomiting (19.4%), and anaemia (13.9%). Three serious AEs (8.3%) led to death in patients given HCQ plus carboplatin/gemcitabine (pulmonary oedema, colitis, and lung infection) but none were caused by the trial treatments; there were no such deaths in the carboplatin–etoposide group. No significant retinal toxicity was noted in HCQ (Supplementary Table 6).

Health-related quality of life (EORTC QLQ-C30 and QLQ-LC13) was similar between the trial groups over time; Supplementary Tables 4–5. HCQ appeared to be associated with increased nausea and vomiting (5.58, 99%CI −2.45, 13.61) but less pain (−10.37, 99%CI −26.50, 5.75). However, these differences were not statistically significant. From the lung cancer module, alopecia appeared to be worse in the HCQ and chemotherapy group (mean difference −20.66, 99%CI −33.32, −8.01) than chemotherapy alone, but with no biological rationale for any such causal link to HCQ.

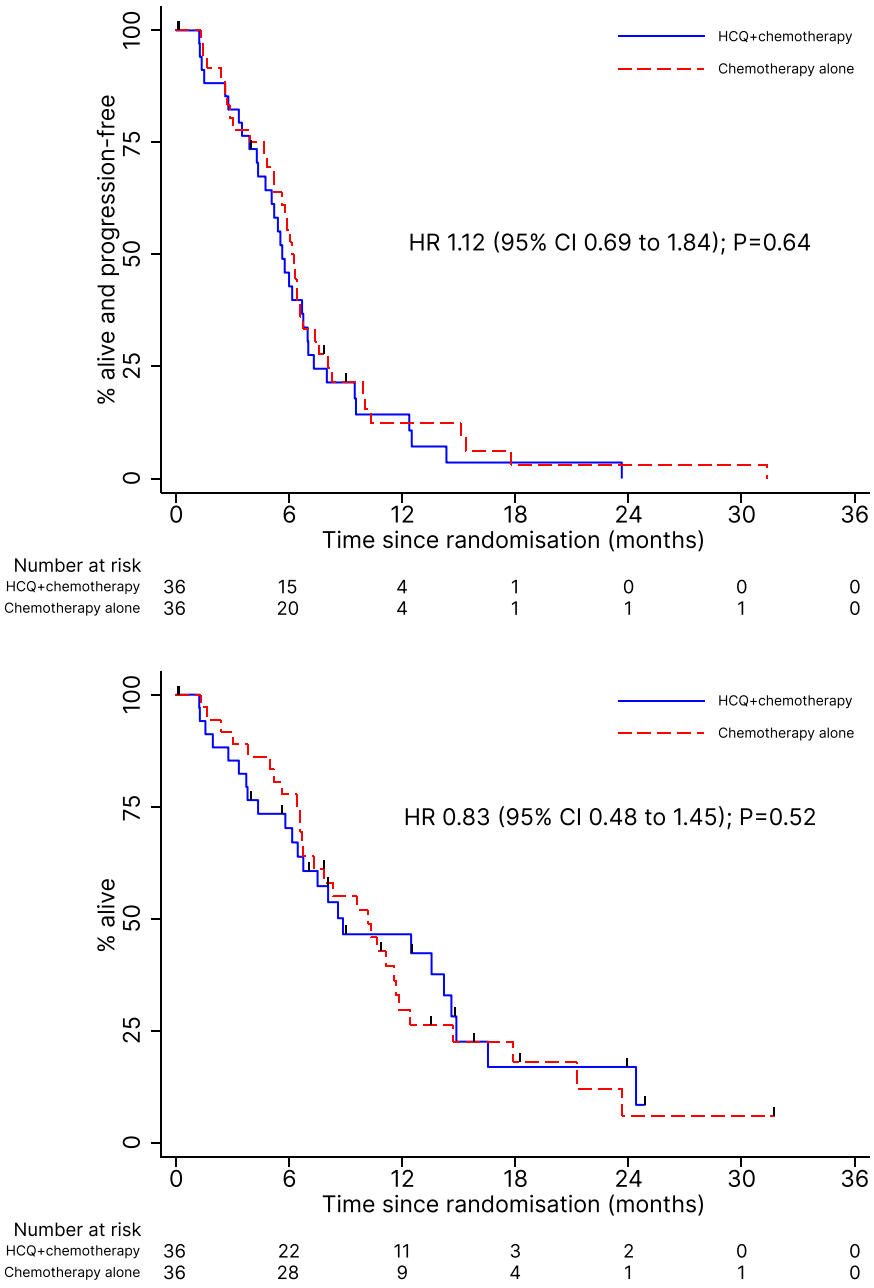

Fig. 2. Kaplan-Meier curves for progression-free survival and overall survival.

5. Discussion

Autophagy has emerged as a significant factor in resistance to several chemotherapeutic agents. We report the first ever trial of an autophagy inhibitor with HCQ in SCLC. Despite using HCQ at doses higher than typically recommended for treating rheumatological disorders, our findings indicate that the addition of HCQ to platinum doublet chemotherapy did not improve efficacy.

Interest in HCQ/chloroquine as potential anti-cancer therapies arises from their effectiveness as autophagy inhibitors, shown in laboratory cell lines [19]. These agents also demonstrate diverse mechanisms of actions, including modulation of TLR9/NF-κB signalling, CXCL12/CXCR4 signalling, p53 pathway, and normalization of tumour vessels to enhance cytotoxic delivery and response in animal models, among other mechanisms, making them promising candidates for cancer therapy [12,19].

Our study contributes to the limited clinical data on HCQ as an anti-cancer agent in lung cancer. A phase I trial of patients with advanced NSCLC on erlotinib shown limited efficacy with HCQ (n = 19), with an ORR of 5%, median PFS of 2 months, and median OS of 10.6 months [20]. Eight patients giving HCQ alone experienced progressive disease [20]. A phase II trial of 30 patients with metastatic NSCLC treated with HCQ, carboplatin and paclitaxel showed an ORR of 33%, with a median PFS of 3.3 months [21]. Another phase II trial with KRAS-mutant NSCLC patients treated with HCQ and binimetinib was halted early due to lack of efficacy (ORR 11%, median PFS 1.9 months, median OS 5.3 months) [22]. These trials, along with our own, confirm that HCQ is not effective in NSCLC or SCLC.

In pancreatic cancer, two small (n = 29 and n = 31) single arm trials of neoadjuvant therapy suggested improvements in survival, [23,24] while another (n = 9) indicated no impact on efficacy [25]. There have been only two randomised trials, both of which evaluated gemcitabine and nab-paclitaxel, with or without HCQ. One study (n = 112) used this combination as first-line therapy for advanced disease and showed no

improvement in either OS or PFS with HCQ. [26] The other (n = 64) of neoadjuvant therapy reported an improvement in histopathological response in the HCQ group but minimal improvements in OS and PFS. [27]

Clinical trials of HCQ in glioblastoma multiforme (glioma) have been summarised elsewhere [28]. Two small randomised studies (18 and 30pts) reported improved OS, but the largest randomised trial (54pts; HCQ plus short-course brain radiotherapy vs radiotherapy alone) showed no effect at all on either PFS or OS [28]. Small trials in other tumours show mixed evidence of activity across breast, [29] colorectal, [30,31] melanoma, [32,33] renal cell, [34] chronic myeloid leukaemia, [35] all solid tumours combined, [36–39] and brain metastases. [40] Considering all clinical trials of HCQ (and occasionally chloroquine) together, the evidence base has not been strong, with most studies being relatively small single arm (early phase) trials. Among the six randomised studies [26–28,35,40] three indicated no effect on efficacy at all, including our Study 15, [26,28] and only one showed improvement in PFS without affecting tumour response or OS.[40]

Study 15 is the first and only randomised multicentre trial on autophagy inhibition in lung cancer. It is also the third largest randomised trial of HCQ across all cancers. The largest trial, involving 112 patients, [26] adding HCQ to gemcitabine and nab-paclitaxel, also did not improve survival among patients with metastatic pancreatic adenocarcinoma.

Currently there are no established predictive biomarkers that can be utilized to find who could benefit from HCQ treatment. A retrospective analysis of two neoadjuvant therapy trials [24,27] suggested that OS and PFS might be better among patients given HCQ who had loss of SMAD4 (a tumour suppressor gene) [41]. Another study found prolonged disease-free survival and OS in pancreatic adenocarcinoma patients who demonstrated a > 51% increase in peripheral blood levels of LC3-II, a marker of autophagy [24]. Elevated plasma levels of Par-4, but not tumour levels of sequestosome-1/p62 (a marker of autophagic flux inhibition), were associated with induced apoptosis in tumour specimens of HCQ-treated patients [37]. Further investigation is needed to understand better patient selection criteria.

Achieving the optimal HCQ dosage for autophagy inhibition presents challenges due to the risk of AEs, particularly retinopathy, when using higher doses for extended periods [42]. It is noteworthy that our trial did not have any cases of retinopathy despite using doses higher than typically recommended for treating rheumatological disorders.

The rates of haematological AEs were notably higher in the HCQ group, particularly when the higher dose of gemcitabine was initially prescribed. The proportion of patients experiencing grade 3–4 anaemia (41.7%) in the HCQ and carboplatin/gemcitabine group is notably higher when compared to other studies [18,27,29]. In our prior large trial of SCLC patients given carboplatin and gemcitabine, grade 3–4 anaemia occurred in only 14%. [18] The rate of neutropenia (30.6%) is consistent with carboplatin/ gemcitabine alone (39%) [18] and when combined with a taxane-doublet (29–43%) [27,30]. The rate of thrombocytopenia (33.3%) appears higher than in other studies (3–22%) [18, 27,30]. Interestingly, neutropenia and thrombocytopenia were dose-limiting toxicities that occurred in a dose-escalation trial of HCQ with carboplatin/gemcitabine in all solid tumours [39]. There may be a link between HCQ and increased haematological toxicities when combined with gemcitabine-based chemotherapy, where several of these AEs were due to our initial use of a higher dose of gemcitabine.

Our trial was halted early by the IDMC for futility, which might be attributed to incomplete tumour autophagy inhibition with a daily dose of 800 mg in our SCLC patients. Compared to other trials using 1000 mg, this dose may be considered low. However, the recommended HCQ dose used was likely appropriate and higher than the standard 200–400mg recommended for rheumatological disorders, considering the poor prognosis and several comorbidities of the SCLC population (21% had performance status 2). Furthermore, the lower PFS and OS may also be due to the HCQ group having fewer chemotherapy cycles due to increased toxicities, some of which were associated with the higher dose of gemcitabine. This is highlighted in the higher percentage of patients (57% compared with 32%) in the higher dose of gemcitabine having reductions, delays, or omissions due to any grade haematological toxicity. Fewer patients in the HCQ group completed at least 4 cycles in general compared with the chemotherapy alone group (64% vs 81%). Notably, seven (19%) patients in the HCQ group discontinued chemotherapy early due to AEs, compared to none in the chemotherapy alone arm. We could have used a different platinum doublet, such as carboplatin and paclitaxel, [43] which is not expected to be contraindicated with HCQ. However, at the time we designed the trial, there was no evidence regarding the combination of these three agents, nor were there any randomised trials comparing first-line carboplatin-paclitaxel with standard platinum-etoposide, in contrast to carboplatin-gemcitabine. We knew that gemcitabine (unlike etoposide) would not be contraindicated when used with HCQ, and we chose gemcitabine because we had direct evidence that it has similar efficacy to etoposide when combined with carboplatin.[18]

More potent and specific autophagy inhibitors are emerging and undergoing pre-clinical development, offering avenues for exploration in future trials that could be guided by biomarkers. Effectiveness could be enhanced by ensuring a more targeted approach and appropriately selected doses.

Our findings underscore the importance of evidence-based medical research and contribute to a more comprehensive understanding of HCQ's repurposing in various medical specialities, given its original use as an anti-malaria agent. This significance is notable in the context of widespread press coverage and political endorsements advocating its use for COVID-19 treatment. The divergence in public narratives emphasizes the need for scientific rigor and careful consideration of the context for HCQ use in drug repurposing efforts. With a focus on cancer treatment, our study adds a more informed understanding of the limitations and potential risks associated with HCQ drug repurposing.

The combination of concurrent and maintenance HCQ (800 mg daily) with platinum doublet chemotherapy did not improve PFS or OS outcomes for extensive-stage SCLC, resulting in more patients stopping chemotherapy early due to increased AEs. While our trial does not provide evidence for HCQ use in SCLC, its significance lies in being the third largest randomised trial of HCQ in any cancer, and the only one in lung cancer. Compared with other randomised studies of HCQ in cancer, the cumulative evidence suggests a limited role of HCQ, and possibly even for autophagy inhibition in cancer treatment. Ongoing or future clinical trials involving autophagy inhibitors should closely monitor efficacy throughout the study and consider early termination for futility if observed.

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CRediT authorship contribution statement

Tanya Ahmad: Writing – review & editing, Resources. **Martin Forster:** Writing – review & editing, Resources. **Madeleine Hewish:** Writing – review & editing, Resources, Project administration. **Robin Rudd:** Writing – review & editing, Funding acquisition. **Eleni Karapanagiotou:** Writing – review & editing, Resources. **Laura Farrelly:** Validation, Project administration, Data curation. **Fiona Blackhall:** Writing – review & editing, Resources, Project administration. **Alastair Greystoke:** Writing – review & editing, Resources, Project administration. **Samreen Ahmed:** Writing – review & editing, Resources, Project administration. **Fion Bremner:** Writing – review & editing, Project administration, Methodology. **Dionysis Papadatos-Pastos:** Writing – review & editing, Resources. **Angel Garcia:** Writing – review & editing, Resources. **Arvind Arora:** Writing – review & editing, Resources.

Simran Vaja: Validation, Formal analysis, Data curation. **Amy Ford:** Writing – review & editing, Resources. **Allan Hackshaw:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation. **Robin Young:** Writing – review & editing, Resources. **Abigail E Hollingdale:** Writing – review & editing, Resources. **Siow Ming Lee:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.115162.

Data availability

On request, the anonymised clinical data can be made available to research groups with an appropriate research plan.

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